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Real-world effectiveness and safety of oral Azvudine versus Paxlovid for COVID-19 in patients with kidney disease: a multicenter, retrospective, cohort study

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Abstract

Background Patients with kidney disease (KD) are at high risk of contracting COVID-19 and developing severe disease. There is still a lack of guidance regarding the treatment of COVID-19 in patients with KD. The safety and effectiveness of Azvudine in treating COVID-19 patients with KD remain unknown.

Methods This study included 32,864 COVID-19 patients from nine centers in Henan Province, China. After applying the exclusion criteria and 2:1 propensity score matching, 438 and 219 participants in the Azvudine and Paxlovid groups, respectively, were subjected to analysis.

Results Kaplan–Meier analysis revealed no significant differences in all-cause death or composite disease progression between the Azvudine and Paxlovid groups (all p values > 0.05). The same results were obtained in the Cox regression analysis after baseline characteristics adjustment. Three different sensitivity analyses contributed to the robustness of these findings. Subgroup analysis revealed that patients treated with Azvudine had a lower risk of composite disease progression than patients treated with Paxlovid did among patients with moderate disease ($p = 0.016$, HR: 0.51, 95% CI: 0.27–0.96). Safety data indicated that there was no difference in the incidence of most adverse events. Compared with the Paxlovid group, the Azvudine group had a lower incidence of hypophosphatemia ($p = 0.008$) and a lower PLT count ($p = 0.045$). Moreover, during the 15-day follow-up since drug administration, higher concentrations of lymphocytes were detected in the Azvudine group.

Conclusions This study is the first to report that the safety and effectiveness of Azvudine are not inferior to those of Paxlovid in COVID-19 patients with KD. This study provides additional treatment options for COVID-19 patients with KD.

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Keywords COVID-19, Kidney diseases, Azvudine, Paxlovid, Real-world, Effectiveness, Safety

Background

In 2019, an estimated 850 million people worldwide had kidney disease (KD), resulting in a significant global economic and health care burden [1, 2]. Chronic kidney disease (CKD) has a higher mortality rate than other common chronic diseases such as cardiovascular disease, stroke, and respiratory disease [3]. In addition to the direct death caused by KD, KD also causes and exacerbates other major noncommunicable diseases, including cardiovascular, cerebrovascular, and chronic respiratory diseases [4]. At present, multiple risk factors for KD have been confirmed, including genetic factors, diabetes, smoking, obesity, hypertension, and aging [4]. The main objectives of KD treatment are to delay the deterioration of renal function, improve or alleviate clinical symptoms, and prevent serious complications [5]. In long-term management, it is important to avoid factors such as infection and inflammation that disrupt the body's balance, which will seriously aggravate the progression of CKD.

At the end of 2019, SARS-CoV-2 swept the world, and the number of patients with coronavirus disease 2019 (COVID-19) surged [6]. After SARS-CoV-2 enters the human body, an inflammatory factor storm occurs in a short period of time, which seriously disrupts the balance of the body and creates considerable challenges for KD patients whose body balance was originally fragile [7]. Compared with healthy controls, patients with KD have a significantly increased rate of severe COVID-19 following infection with SARS-CoV-2 [8]. KD is the most common risk factor for death in COVID-19 patients worldwide, and its risk increases as the stage of CKD increases [9].

There is still a lack of guidance regarding the treatment of COVID-19 in patients with KD. In addition to symptomatic and supportive treatment, antiviral treatment is an important component of the fight against COVID-19. In early management of COVID-19, the use of monoclonal antibodies (mAbs) to block the binding of the spike protein receptor-binding domain (RBD) on SARS-CoV-2 to the human angiotensin-converting enzyme 2 (ACE2) receptor on cells was reported to be an effective treatment [10]. However, the application of monoclonal antibodies is limited by a variety of factors including viral mutations [11] and genetic polymorphisms [12]. Currently, the common antiviral treatment drugs in China are Paxlovid and Azvudine [13, 14], which are robust and unlikely to be affected by the above limitations. In clinical trials of COVID-19 patients without comorbidities, patients treated with either Paxlovid or Azvudine had better outcomes compared with those who did not receive drug treatment [15–18]. Retrospective cohort studies from China compared the efficacy of Paxlovid and Azvudine in hospitalized patients with COVID-19. The results showed that Azvudine could significantly reduce the incidence of composite disease progression compared with Paxlovid, and there was no difference in the incidence of all-cause mortality between the two drugs [19, 20].

However, despite their high risk, patients with severe kidney impairment have been excluded from clinical trials of treatments for COVID-19, primarily because of their increased risk of death. Patients with mild and toxic kidney damage should be treated with caution under the guidance of doctors. In addition, studies have reported that Azvudine not only inhibits SARS-CoV-2 replication but also regulates the body's immune response [18]. To date, the safety and effectiveness of Azvudine for treating COVID-19 in patients with KD remain unknown.

In this study, a large-scale, multicenter, retrospective, real-world cohort study was conducted on COVID-19 patients with KD. The effectiveness and safety of oral Azvudine and Paxlovid were also evaluated. Multiple sensitivity analyses were performed to verify these findings.

Methods

Study design and participants

This was a multicenter, observational, retrospective cohort study. A total of 32,864 hospitalized patients diagnosed with SARS-CoV-2 infection between December 5, 2022, and January 31, 2023, in Henan Province, China, were included in this study. The participants in this study were recruited from nine centers, including the First Affiliated Hospital of Zhengzhou University, Henan Infectious Disease Hospital, Henan Provincial Chest Hospital, Shangqiu Municipal Hospital, Fifth People's Hospital of Anyang, Nanyang Central Hospital, Luoyang Central Hospital, Guangshan County People's Hospital, and Fengqiu County People's Hospital. The ethics committee approved this study, and a detailed ethical statement can be found in the Supplementary Methods. This study was a retrospective study, and all the patients were anonymous and there was no need for individual informed consent.

All participants in this study were diagnosed by a positive SARS-CoV-2 nucleic acid test. All participants in this study had a history of kidney disease before being diagnosed with COVID-19, and those who developed kidney disease after infection with SARS-CoV-2 were excluded. In this study, kidney diseases included nephritic syndrome, nephrotic syndrome, renal insufficiency, renal failure, kidney transplant, renal tumors, renal cysts,

kidney stones, renal vascular disease, polycystic kidney disease, and renal hamartoma.

The exclusion criteria were as follows: (1) participants under 18 years of age; (2) pregnant women; (3) participants who did not receive antiviral treatment; (4) participants who received other antiviral agents; (5) participants who had contraindications to Azvudine or Paxlovid (the detailed contraindications to Azvudine or Paxlovid can be found in the Supplementary Methods); and (6) participants who did not have kidney diseases. All patients were diagnosed and treated according to the " COVID-19 diagnosis and treatment plan (trial version 9 or version 10)" issued by the National Health Commission of China [13, 14].

Data sources

The demographic and clinical characteristics of the participants were obtained from the hospital's electronic medical record (EMR) system. The clinical characteristics included admission and discharge dates, diagnosis, medication information, imaging data, laboratory test data, ICU admission, and registered death.

Procedures

The study was conducted in accordance with the STROBE guidelines and the ethical standards outlined in the 1975 Declaration of Helsinki. Experienced doctors prescribe drugs to patients, including Paxlovid (glomerular filtration rate (GFR) ≥ 60 ml/min, nirmatrelvir 300 mg and ritonavir 100 mg once every 12 h for 5 days; GFR < 60 ml/min, nirmatrelvir 150 mg and ritonavir 100 mg once every 12 h for 5 days) or Azvudine (5 mg once daily for up to 14 days) or other treatment options [13, 14]. We divided patients into the Azvudine group and the Paxlovid group on the basis of their drug prescriptions in the EMR system. The observations in this study started at the time of diagnosis of SARS-CoV-2 infection and continued for 31 days.

Outcomes

The primary outcome of this study was all-cause death. Death information was obtained from the hospital's electronic medical records system. The secondary outcome of this study was composite disease progression, which was defined as progression to severe disease or death in patients with mild or moderate disease or death. Disease severity was defined according to the " COVID-19 diagnosis and treatment plan (trial version 9 or version 10)" issued by the National Health Commission of China [13, 14]. Mild disease was defined as upper respiratory tract symptoms, such as a dry throat, sore throat, cough, and fever, as the main manifestation. Moderate disease was defined as persistent high fever for > 3 days and/or cough, shortness of breath, etc., but the respiratory rate was < 30 breaths/min, and the oxygen saturation when breathing air at rest was > 93%. Imaging revealed characteristic symptoms of pneumonia caused by COVID-19. Severe disease was defined as a respiratory rate ≥ 30 beats/minute, an oxygen saturation ≤ 93% when breathing air at rest, a PaO2/FiO2 ≤ 300 mmHg, or imaging showing lung disease progression > 50% in 24–48 h, or the need for mechanical ventilation, or shock, or intensive care unit (ICU) monitoring.

Safety outcomes were evaluated on the basis of overall adverse events (AEs) and grade ≥ 3 AEs. We defined adverse events according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0) [21]. This study focused on the characteristics of the laboratory tests used to assess adverse events. AEs were observed from the time of administration until the end of 5 half-lives after the last dose. We used the most severe grade for subsequent analyses when the participants experienced adverse events of different grades.

Definition of covariates

Demographic data such as sex, age, and body mass index (BMI) were obtained from an electronic medical record system. All participants were classified as "mild," "moderate," or "severe" according to the severity of the disease on the basis of their clinical characteristics at admission combined with the "COVID-19 diagnosis and treatment plan (trial version 9 or version 10)" [13, 14]. Concomitant systemic steroids were defined as "no" or "yes" according to the receipt of systemic steroids within one day of admission. The time from diagnosis to treatment exposure was defined as "0–5 days" or ">5 days", according to the period from the date of diagnosis of COVID-19 to the date of first treatment with Azvudine or Paxlovid. Laboratory test data, including routine blood tests (white blood cells (WBC), neutrophils (Neut), lymphocytes (Lymph), eosinophils (Eos), basophils (Baso), and monocytes (Mono)), liver function (aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), albumin (ALB), alkaline phosphatase (ALP), total bilirubin (TBIL), glucose (Glu), triglyceride (TG), alanine cholesterol (CH), low-density lipoprotein (LDL), high-density lipoprotein (HDL), renal function (glomerular filtration rate (GFR) and creatinine (CREA)), coagulation function (procalcitonin (PCT) and C–reactive protein (CRP)) and inflammatory indicators (activated partial thromboplastin time (APTT) and prothrombin time (PT)), were recorded from the data collected on the day of diagnosis of COVID-19. Comorbidities such as cardiovascular diseases, cerebrovascular diseases, liver diseases, hypertension, diabetes, and primary malignant tumors were obtained from the electronic medical records system.

Statistical analysis

R software version 4.0.3 was used for statistical analysis in this study. Continuous variables are described statistically as the mean (standard deviation) or median (interquartile range) depending on whether they were normally distributed, and differences were analyzed using the independent t test or Mann–Whitney U test. Categorical variables are described statistically as counts and percentages, and differences were analyzed using the chi-square test. Missing values were imputed using multiple imputations, and the detailed data interpolation process can be found in the Supplementary Methods (Table S1). Propensity score matching (PSM) was used to match the Paxlovid and Azvudine groups at a ratio of 1:2. A greedy matching method of 1:2 was used to control for baseline covariates in the logistic regression model to reduce the influence of confounding factors on the outcomes. Cumulative event curves were generated using the Kaplan–Meier method, and the log-rank test was used to determine survival differences between the groups. Primary and secondary outcomes were evaluated using hazard ratios (HRs) with 95% confidence intervals (CIs) from Cox proportional hazards regression models, and all baseline covariates were adjusted. Schoenfeld residuals were used to evaluate the proportional hazards assumption. The variance inflation factor (VIF) was calculated to identify multicollinearity, and a VIF value > 5 was defined as multicollinearity. A subgroup analysis was performed using covariates.

A sensitivity analysis was conducted to ensure the robustness and reliability of the findings. First, a narrowing-down population method that excluded participants who were discharged or died on the first day of administration was used for the subsequent analysis. Second, a probit model was used for 1:2 greedy matching. Third, we used mean imputation to replace the above multiple imputation for the missing values and then used 1:1 greedy matching to replace the above 1:2 greedy matching. A 2-sided p value < 0.05 was considered statistically significant.

Results

Study profile and baseline characteristics

In this study, 32,864 hospitalized patients with COVID-19 from nine centers in Henan Province, China, were included. Through strict inclusion and exclusion criteria, 831 COVID-19 patients with KD treated with Azvudine and 219 COVID-19 patients with KD treated with Paxlovid were screened out (Fig. 1, Table S2). Through analysis, we found that there were differences in the baseline characteristics between the Azvudine and Paxlovid groups (Table 1, Figure S1). A lower age ($p = 0.026$), percentage of males ($p = 0.02$), time from diagnosis to treatment exposure ($p < 0.001$), incidence of liver diseases ($p < 0.001$), cardiovascular diseases ($p = 0.003$), Neut ($p < 0.001$), ALT ($p = 0.01$), and GFR ($p = 0.039$) and higher levels of concomitant systemic steroids ($p = 0.021$), creatinine ($p = 0.001$), and PT ($p = 0.041$) were observed in the Azvudine group than in the Paxlovid group. We used 2:1 PSM to ensure that the two groups had the same baseline characteristics. Finally, 438 participants in the Azvudine group and 219 participants in the Paxlovid group with matched baseline characteristics were used for subsequent analysis (all p values > 0.05) (Table S3).

Primary outcome and secondary outcome

The primary outcome was all-cause death. We used Kaplan–Meier analysis and the log-rank test to compare all-cause death between the two groups. During the 31-day observation period from the first day of treatment, a total of 79 deaths occurred in the Azvudine group, and 51 deaths occurred in the Paxlovid group (Figs. 2A and 3). At the end of the observation period, 35 participants in the Azvudine group and 17 in the Paxlovid group did not die or were discharged. There was no difference in all-cause death between the two groups ($p = 0.1$). Cox regression analysis with multivariate adjustment was performed to compare the risk between the two groups. Compared with the Paxlovid group, the HR for all-cause mortality in the Azvudine group was 0.82 (95% CI: 0.562-1.200) ($p = 0.309$) (Fig. 3).

The secondary outcome of this study was composite disease progression. The Kaplan–Meier analysis and log-rank test revealed 122 progressions in the Azvudine group and 69 progressions in the Paxlovid group during the 31-day observation period (Figs. 2B and 3). The composite disease progression-free curve revealed no significant difference in composite disease progression between the two groups ($p = 0.35$). Cox regression analysis revealed that the HR for composite disease progression in the Azvudine group was 1.05 (95% CI: 0.761–1.439) versus that in the Paxlovid group ($p = 0.781$) (Fig. 3).

Moreover, we calculated the variance inflation factor (VIF) to assess the degree of multicollinearity in the model. The results revealed that each VIF was less than 5, indicating that the model was reliable. In summary, there was no difference in all-cause death or composite disease progression between Azvudine and Paxlovid in COVID-19 patients with KD. This means that Azvudine and Paxlovid have the same effectiveness in the population of COVID-19 patients with KD.

Subgroup analysis

Additionally, we performed a subgroup analysis to clarify the associations between antiviral treatment, all-cause death, and composite disease progression. Multivariate Cox regression analysis was used to evaluate the interaction effects between the groups. The results revealed that

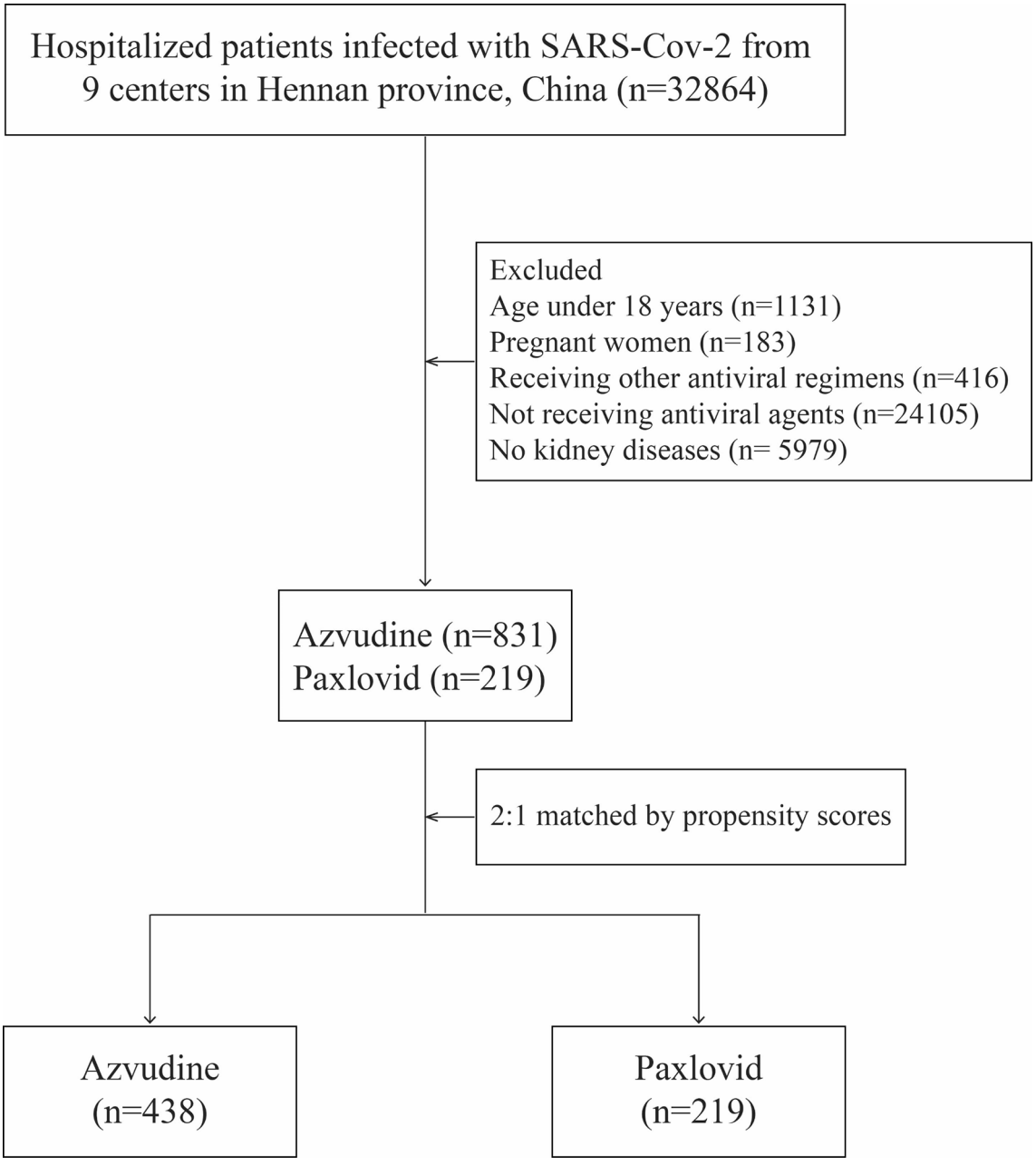


Fig. 1 The flowchart of study design. In this study, a total of 32,864 COVID-19 hospitalized patients from 9 centers in Henan Province, China were included. Through strict inclusion and exclusion criteria, 831 COVID-19 patients with KD treated with Azvudine and 219 COVID-19 patients with KD treated with Paxlovid were screened out. Based on a 2:1 propensity score matching, 438 participants in Azvudine group and 219 participants in Paxlovid group were subjected to subsequent analysis

sex, age, severity at admission, concomitant hormone therapy, time from diagnosis to treatment, diabetes status, hypertension status, liver diseases, cardiovascular diseases, cerebrovascular diseases, and primary malignant tumors were not associated with all-cause mortality during treatment with either of the two antiviral drugs (all p values for interaction > 0.05) (Fig. 4). We subsequently evaluated the associations between these factors and composite disease progression. The results indicated that moderate disease had an interaction effect with composite disease progression (p for interaction = 0.038). The risk of composite disease progression in patients with moderate disease receiving Azvudine was significantly decreased (HR: 0.51, 95% CI: 0.27–0.96). In addition, the 95% CI of the mild group was 0-Inf, which may be related to the small proportion of mild patients. In summary, the subgroup analysis revealed that receiving Azvudine or Paxlovid did not interact with all-cause death, and

Table 1 Baseline characteristics of COVID-19 patients with kidney diseases before and after propensity score matching

Characteristics	Before matching			After 2:1 matching		
	Azvudine (*n* = 831)	Paxlovid (*n* = 219)	*P* value	Azvudine (*n* = 438)	Paxlovid (*n* = 219)	*P* value
Age, mean (SD), year	67.33 (15.28)	69.92 (15.48)	0.026	68.89 (14.97)	69.92 (15.48)	0.409
Gender, n (%)			0.02			0.822
Male	564 (67.9)	167 (76.3)		329 (75.1)	167 (76.3)	
Female	267 (32.1)	52 (23.7)		109 (24.9)	52 (23.7)	
BMI, mean (SD), kg/m^2	24.23 (4.18)	24.25 (3.80)	0.957	24.36 (4.27)	24.25 (3.80)	0.746
Severity at admission, n (%)			0.055			0.971
Mild	62 (7.5)	12 (5.5)		26 (5.9)	12 (5.5)	
Moderate	487 (58.6)	114 (52.1)		228 (52.1)	114 (52.1)	
Severe	282 (33.9)	93 (42.5)		184 (42.0)	93 (42.5)	
Time from diagnosis to treatment exposure, n (%)			< 0.001			0.111
> 5 days	162 (19.5)	86 (39.3)		143 (32.6)	86 (39.3)	
0–5 days	669 (80.5)	133 (60.7)		295 (67.4)	133 (60.7)	
Concomitant systemic steroid, n (%)			0.021			0.793
No	484 (58.2)	147 (67.1)		288 (65.8)	147 (67.1)	
Yes	347 (41.8)	72 (32.9)		150 (34.2)	72 (32.9)	
Comorbidities, n (%)						
Diabetes	277 (33.3)	66 (30.1)	0.414	131 (29.9)	66 (30.1)	1
Hypertension	493 (59.3)	119 (54.3)	0.21	254 (58.0)	119 (54.3)	0.419
Liver diseases	127 (15.3)	65 (29.7)	< 0.001	101 (23.1)	65 (29.7)	0.081
Cardiovascular diseases	193 (23.2)	73 (33.3)	0.003	133 (30.4)	73 (33.3)	0.494
Cerebrovascular diseases	104 (12.5)	33 (15.1)	0.376	66 (15.1)	33 (15.1)	1
Primary malignant tumor	63 (7.6)	23 (10.5)	0.206	44 (10.0)	23 (10.5)	0.964
Laboratory parameters, mean (SD)						
Neutrophil, ×10^9/L	6.42 (4.31)	7.99 (5.77)	< 0.001	7.39 (4.80)	7.99 (5.77)	0.162
Lymphocyte, ×10^9/L	0.85 (0.59)	0.77 (1.12)	0.157	0.85 (0.63)	0.77 (1.12)	0.246
Glucose, mmol/L	9.24 (5.81)	9.09 (5.22)	0.745	9.05 (5.56)	9.09 (5.22)	0.925
High-density lipoprotein, mmol/L	0.99 (0.33)	0.99 (0.32)	0.987	0.99 (0.34)	0.99 (0.32)	0.857
Low-density lipoprotein, mmol/L	2.06 (0.95)	2.19 (1.02)	0.073	2.12 (1.02)	2.19 (1.02)	0.363
Alanine aminotransferase, IU/L	33.33 (70.44)	49.02 (109.23)	0.01	36.62 (76.08)	49.02 (109.23)	0.091
Aspartate aminotransferase, IU/L	44.88 (100.46)	50.73 (89.29)	0.434	43.37 (72.68)	50.73 (89.29)	0.258
Creatine, μmol/L	288.11 (368.98)	201.28 (241.18)	0.001	210.21 (254.94)	201.28 (241.18)	0.667
Glomerular filtration rate, ml/min	48.08 (36.19)	53.74 (35.48)	0.039	51.77 (35.58)	53.74 (35.48)	0.504
C-reactive protein, mg/L	69.52 (84.40)	68.18 (67.39)	0.829	68.37 (79.13)	68.18 (67.39)	0.976
Procalcitonin, ng/ml	2.41 (8.99)	3.64 (11.93)	0.095	3.14 (11.40)	3.64 (11.93)	0.606
Prothrombin time, s	18.56 (14.49)	16.33 (14.07)	0.041	16.41 (11.68)	16.33 (14.07)	0.934
Activated partial thromboplastin time, s	26.60 (12.85)	28.41 (18.14)	0.092	28.39 (13.33)	28.41 (18.14)	0.989
Cholesterol, mmol/L	3.83 (1.13)	3.85 (1.16)	0.822	3.82 (1.17)	3.85 (1.16)	0.761
Triglyceride, mmol/L	1.58 (1.01)	1.48 (0.86)	0.196	1.48 (0.72)	1.48 (0.86)	0.999
Alkaline phosphatase, IU/L	87.64 (63.47)	92.83 (63.76)	0.282	91.02 (56.25)	92.83 (63.76)	0.71
Gamma-glutamyl transpeptidase, IU/L	56.96 (77.51)	64.36 (86.25)	0.22	63.70 (93.62)	64.36 (86.25)	0.931
Albumin, g/L	35.94 (65.98)	31.56 (8.34)	0.328	31.47 (10.59)	31.56 (8.34)	0.911
Total bilirubin, μmol/L	10.67 (10.11)	11.20 (8.87)	0.481	10.47 (9.15)	11.20 (8.87)	0.331

receiving Azvudine in patients with moderate disease was associated with a lower risk of composite disease progression.

Sensitivity analyses

First, the narrowing-down population method was used to exclude participants who were discharged or died on the first day of administration. After screening, 416 and 213 participants in the Azvudine and Paxlovid groups, respectively, were analyzed (Table S4). During the 31-day observation period, 80 deaths occurred in the Azvudine group, and 50 deaths occurred in the Paxlovid group (Figure S2A, Figure S3). Kaplan–Meier analysis and the log-rank test revealed no significant differences in

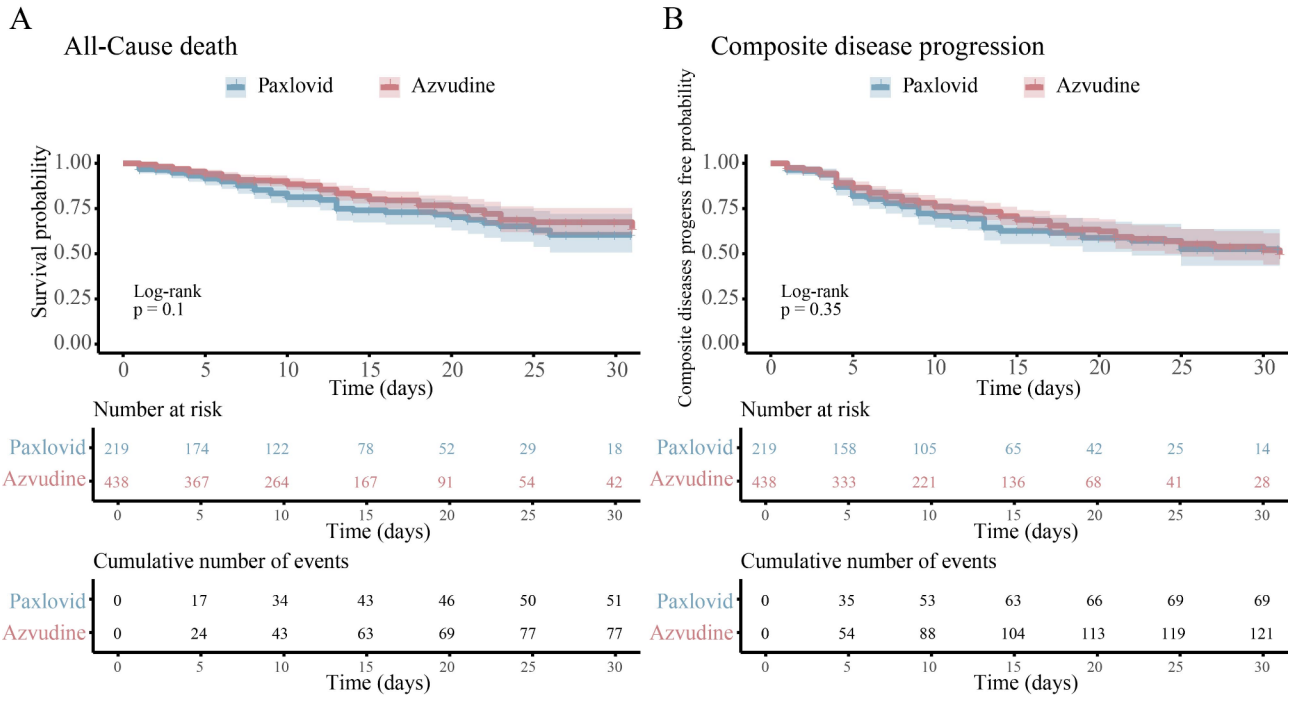


Fig. 2 Kaplan–Meier curves of COVID-19 patients with kidney diseases receiving Azvudine versus Paxlovid. (**A**) Cumulative hazard of all-cause death and (**B**) composite disease progression

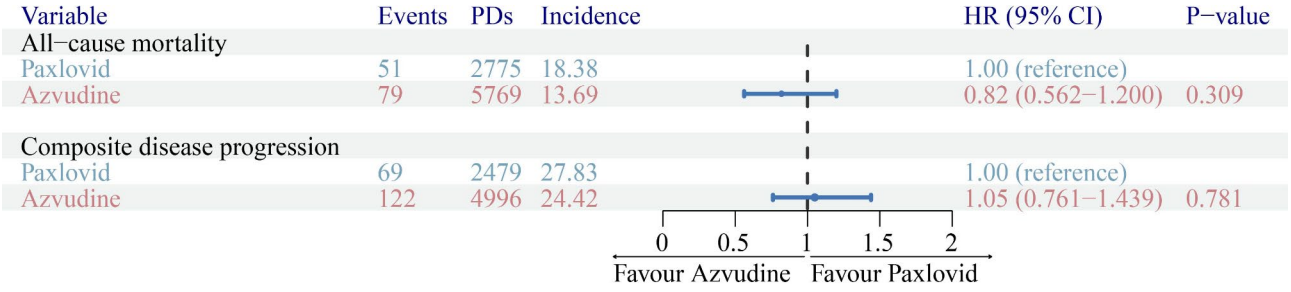


Fig. 3 Multivariate Cox proportional hazards regression analysis of all-cause death and composite disease progression in COVID-19 patients with kidney diseases receiving Azvudine versus Paxlovid. Adjusted for all baseline covariates in Table 1. HR: Hazard Ratio; 95%CI: 95% confidence interval. PDs: Person-days. Incidence: events/per 1000 PDs

all-cause death ($p = 0.22$) or composite disease progression ($p = 0.45$) between the two groups (Figure S2B). In addition, Cox regression analysis revealed no significant differences in all-cause mortality ($p = 0.182$, HR: 0.78, 95% CI: 0.535–1.126) or composite disease progression ($p = 0.487$, HR: 0.89, 95% CI: 0.650–1.228) between the two groups (Figure S3).

Second, a probit model was used for the 1:1 greedy matching (Table S5). Survival curves generated via Kaplan–Meier analysis revealed that all-cause death ($p = 0.11$) and composite disease progression ($p = 0.23$) were similar between the Azvudine and Paxlovid groups (Figure S4). Moreover, the results of Cox regression analysis also revealed no difference ($p = 0.327$, HR: 0.83, 95% CI: 0.568–1.207; $p = 0.996$, HR: 1.00, 95% CI: 0.725–1.376) (Figure S5).

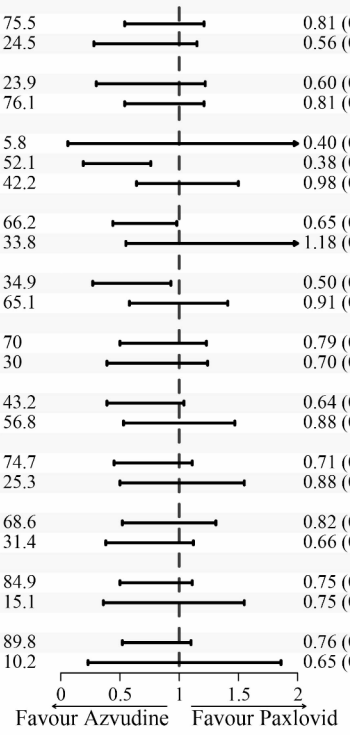
Third, the missing values were imputed with the mean value, and 1:1 greedy matching was performed (Table S6). Eighty deaths occurred in the Azvudine group, and 51 deaths occurred in the Paxlovid group (Figure S6A). Through Kaplan–Meier analysis, a p value of 0.11 was obtained for all-cause death between the two groups, and a p value of 0.23 was obtained for composite disease progression (Figure S6B). All-cause death was subsequently analyzed by Cox regression analysis, and the HR of the Azvudine group was 0.78 (95% CI: 0.536–1.125) compared with that of the Paxlovid group ($p = 0.181$). A p value of 0.904 was reached for composite disease progression (Figure S7).

In summary, the results obtained by the sensitivity analyses were consistent with the original results, indicating the robustness and reliability of our findings.

A

All-Cause death

Variable	Count	Percent	HR (95% CI)	P-value	P for interaction
Gender					0.45
Male	496	75.5	0.81 (0.54-1.21)	0.304	
Femal	161	24.5	0.56 (0.28-1.15)	0.116	
Age					0.448
<=60 Year	157	23.9	0.60 (0.30-1.22)	0.155	
>60 Year	500	76.1	0.81 (0.54-1.21)	0.302	
Severity at admission					0.064
Mild	38	5.8	0.40 (0.06-2.85)	0.358	
Moderate	342	52.1	0.38 (0.19-0.76)	0.006	
Severe	277	42.2	0.98 (0.64-1.50)	0.918	
Concomitant hormone therapy					0.182
No	435	66.2	0.65 (0.44-0.98)	0.038	
Yes	222	33.8	1.18 (0.55-2.53)	0.68	
Time from diagnosis to treatment exposure					0.118
>5 Day	229	34.9	0.50 (0.27-0.93)	0.029	
<=5 Day	428	65.1	0.91 (0.58-1.41)	0.664	
Diabetes					0.731
No	460	70	0.79 (0.50-1.23)	0.296	
Yes	197	30	0.70 (0.39-1.24)	0.216	
Hypertension					0.376
No	284	43.2	0.64 (0.39-1.04)	0.072	
Yes	373	56.8	0.88 (0.53-1.47)	0.631	
Liver diseases					0.552
No	491	74.7	0.71 (0.45-1.11)	0.137	
Yes	166	25.3	0.88 (0.50-1.55)	0.657	
Cardiovascular diseases					0.51
No	451	68.6	0.82 (0.52-1.31)	0.415	
Yes	206	31.4	0.66 (0.38-1.12)	0.125	
Cerebrovascular diseases					0.955
No	558	84.9	0.75 (0.50-1.11)	0.152	
Yes	99	15.1	0.75 (0.36-1.55)	0.43	
Primary malignant tumor					0.859
No	590	89.8	0.76 (0.52-1.10)	0.143	
Yes	67	10.2	0.65 (0.23-1.86)	0.425	



B

Composite disease progression

Variable	Count	Percent	HR (95% CI)	P-value	P for interaction
Gender					0.725
Male	496	75.5	0.84 (0.60-1.18)	0.322	
Femal	161	24.5	0.92 (0.49-1.71)	0.789	
Age					0.164
<=60 Year	157	23.9	0.58 (0.30-1.10)	0.094	
>60 Year	500	76.1	0.96 (0.69-1.34)	0.822	
Severity at admission					0.016
Mild	38	5.8	0.00 (0.00-Inf)	0.999	
Moderate	342	52.1	0.51 (0.27-0.96)	0.038	
Severe	277	42.2	1.05 (0.75-1.48)	0.774	
Concomitant hormone therapy					0.225
No	435	66.2	0.74 (0.51-1.07)	0.113	
Yes	222	33.8	1.09 (0.66-1.81)	0.743	
Time from diagnosis to treatment exposure					0.758
>5 Day	229	34.9	0.92 (0.57-1.51)	0.754	
<=5 Day	428	65.1	0.83 (0.57-1.20)	0.317	
Diabetes					0.526
No	460	70	0.93 (0.65-1.33)	0.675	
Yes	197	30	0.76 (0.45-1.27)	0.288	
Hypertension					0.258
No	284	43.2	0.73 (0.48-1.11)	0.136	
Yes	373	56.8	1.03 (0.67-1.57)	0.898	
Liver diseases					0.884
No	491	74.7	0.89 (0.62-1.27)	0.517	
Yes	166	25.3	0.84 (0.49-1.43)	0.516	
Cardiovascular diseases					0.809
No	451	68.6	0.89 (0.61-1.29)	0.543	
Yes	206	31.4	0.84 (0.51-1.36)	0.469	
Cerebrovascular diseases					0.75
No	558	84.9	0.89 (0.64-1.23)	0.471	
Yes	99	15.1	0.77 (0.39-1.52)	0.457	
Primary malignant tumor					0.933
No	590	89.8	0.86 (0.63-1.17)	0.345	
Yes	67	10.2	0.88 (0.33-2.40)	0.808	

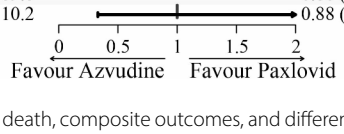


Fig. 4 Subgroup analyses for the association between all-cause death, composite outcomes, and different antiviral treatments in COVID-19 patients with kidney diseases. (**A**) Hazard Ratio of all-cause death. (**B**) Hazard Ratio of composite disease progression. HR: Hazard Ratio; 95%CI: 95% confidence interval

Safety

Adverse events during follow-up were used to evaluate safety (Table 2). The results revealed that there was no difference between the treatment groups in the incidence of most adverse events. Compared with the Paxlovid group, the Azvudine group had a lower incidence of hypophosphatemia ($p = 0.008$) and a lower PLT count ($p = 0.045$). There was no significant difference in the incidence of grade ≥ 3 adverse events between the two groups. In summary, Azvudine had a lower incidence of adverse events than Paxlovid did.

Dynamic alterations in leukocyte subsets

A previous study reported that Azvudine could promote thymic function and improve the lymphocyte spectrum [18, 22, 23]. Therefore, we further analyzed the dynamic alterations in leukocyte subsets within 15 days of drug administration. During the 15-day follow-up period, white blood cells and neutrophils remained above the normal range, lymphocytes and eosinophils remained below the normal range, and basophils and monocytes remained within the normal range (Fig. 5). When comparing lymphocyte counts between the two groups, during the entire observation period, there were 13 days when the mean lymphocyte count of the Azvudine group was greater than that of the Paxlovid group, and the difference was statistically significant on day 2 (Azvudine group: 0.62 (mean), 95% confidence interval = 0.54 to 0.7; Paxlovid group: 0.46 (mean), 95% confidence interval = 0.39 to 0.52; $p = 0.0087$) and day 9 (Azvudine group: 0.91 (mean), 95% confidence interval = 0.75 to 1.08; Paxlovid group: 0.56 (mean), 95% confidence interval = 0.45 to 0.67; $p = 0.0046$). In summary, Azvudine significantly increased lymphocyte counts compared with Paxlovid in COVID-19 patients with KD.

Discussion

The rapid spread of SARS-CoV-2 has led to many deaths worldwide [6, 24]. Owing to the use of immunosuppressants, the imbalance of inflammatory factors, and other reasons, KD patients have significantly higher disease susceptibility and disease severity rates than healthy people do [25]. There are currently no COVID-19 treatment guidelines for patients with KD. Therefore, there is an urgent need to identify suitable therapeutic drugs for COVID-19 patients with KD. In China, the antiviral drugs recommended by the diagnosis and treatment guidelines for COVID-19 patients without any comorbidities are Azvudine and Paxlovid [13, 14, 26–28]. However, the effectiveness and safety of Azvudine in COVID-19 patients with KD remain unknown. Therefore, this multicenter retrospective, real world, cohort study was conducted in Henan Province, China. We matched COVID-19 patients with KD who received Azvudine and Paxlovid, compared all-cause death and composite disease progression, and further evaluated the incidence of adverse events between the two groups. Our findings indicated that the effectiveness and safety of Azvudine in COVID-19 patients with KD were not inferior to those of Paxlovid. This study is the first to clarify the effectiveness

Table 2 Incidence of adverse event of COVID-19 patients receiving Azvudine and Paxlovid

Adverse events (*n*, %)	Available data[a]		All grades			Grade ≥ 3[b]		
	Azvudine	Paxlovid	Azvudine	Paxlovid	*P* value	Azvudine	Paxlovid	*P* value
ALT increased	257	157	77 (30%)	50 (32%)	0.7	12 (4.7%)	7 (4.5%)	> 0.9
AST increased	270	161	81 (30%)	49 (30%)	> 0.9	13 (4.8%)	6 (3.7%)	0.6
ALP increased	256	157	32 (13%)	21 (13%)	0.8	0 (0%)	1 (0.6%)	0.4
GGT increased	223	152	44 (20%)	37 (24%)	0.3	4 (1.8%)	2 (1.3%)	> 0.9
Hyperuricemia	249	155	33 (13%)	19 (12%)	0.8	0 (0%)	0 (0%)	
Hypophosphatemia	161	117	20 (12%)	29 (25%)	0.008	0 (0%)	0 (0%)	
Hypokalemia	299	174	73 (24%)	37 (21%)	0.4	30 (10%)	15 (8.6%)	0.6
Hyperkalemia	299	174	28 (9.4%)	14 (8.0%)	0.6	2 (0.7%)	1 (0.6%)	> 0.9
Hypercholesterolemia	73	20	9 (12%)	2 (10%)	> 0.9	0 (0%)	0 (0%)	
Hypertriglyceridemia	63	20	22 (35%)	4 (20%)	0.2	2 (3.2%)	0 (0%)	> 0.9
Hypoglycemia	55	7	6 (11%)	1 (14%)	> 0.9	0 (0%)	0 (0%)	
CREA increased	278	161	65 (23%)	44 (27%)	0.4	21 (7.6%)	11 (6.8%)	0.8
Lymphocyte count decreased	383	185	174 (45%)	85 (46%)	> 0.9	120 (31%)	73 (39%)	0.055
Lymphocyte count increased	383	185	8 (2.1%)	3 (1.6%)	> 0.9	1 (0.3%)	0 (0%)	> 0.9
PLT count decreased	276	164	59 (21%)	49 (30%)	0.045	26 (9.4%)	22 (13%)	0.2
Neutrophil count increased	230	158	13 (5.7%)	9 (5.7%)	> 0.9	3 (1.3%)	3 (1.9%)	0.7
Anemia	237	161	117 (49%)	83 (52%)	0.7	50 (21%)	39 (24%)	0.5

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT Glutamyltransferase; PLT, platelets; CREA, creatinine

[a]: Number of people who completed follow-up data collection for this indicator

[b]: Severity grades were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

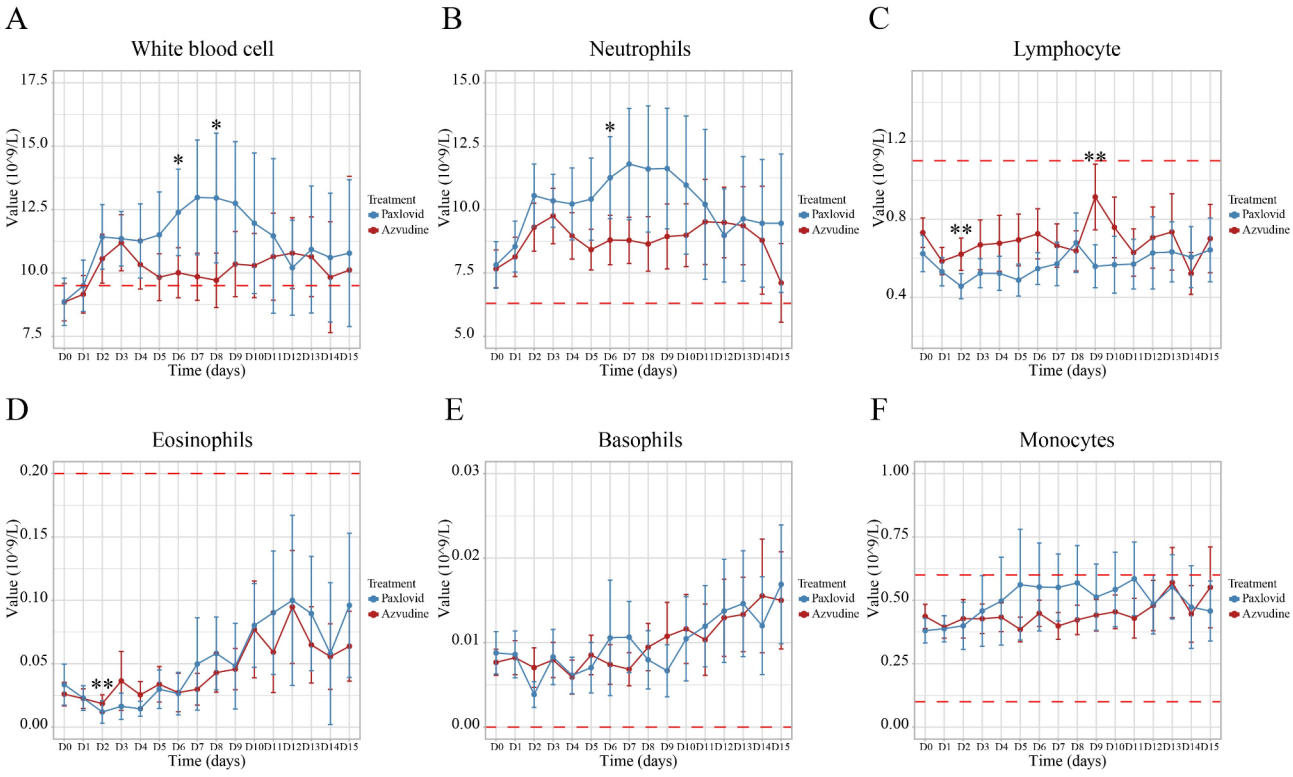


Fig. 5 Dynamic alterations of leukocyte subsets during the treatment process in COVID-19 patients with kidney diseases. During the 15-day follow-up period, dynamic alterations of (**A**) white blood cells, (**B**) neutrophils, (**C**) lymphocytes, (**D**) eosinophils, (**E**) basophils and (**F**) monocytes were analyzed. *, $p < 0.05$; **, $p < 0.01$

and safety of Azvudine in COVID-19 patients with KD. Our findings provide evidence for the clinical treatment of COVID-19 patients with KD.

The effectiveness of Paxlovid in COVID-19 patients with KD has been reported in previous studies [29, 30]. Compared with the absence of antiviral drugs, Paxlovid is strongly effective and can significantly reduce all-cause death, the incidence of lung infection, and the duration of SARS-CoV-2 elimination. However, the effectiveness of Azvudine in COVID-19 patients with KD remains unknown. Therefore, in this study, we confirmed that the effects of Azvudine on all-cause death and composite disease progression in COVID-19 patients with KD were not different from those of Paxlovid through a large-sample real-world study in nine centers. In addition, Azvudine significantly reduced composite disease progression compared with Paxlovid in moderate patients. To improve the robustness of the findings of this study, three sensitivity analyses were performed, and the results were consistent with the original findings. Therefore, for the first time, we reported that the effectiveness of Azvudine in COVID-19 patients with KD was not inferior to that of Paxlovid.

Considering the use of immunosuppressants, internal environmental disorders, and comorbidities in patients with KD, the safety of antiviral drugs has attracted much attention [31]. One study reported that after 7- days of Paxlovid administration, the plasma creatinine concentration of COVID-19 patients with KD did not change significantly [30]. However, in kidney transplant patients, the half-life of tacrolimus during Paxlovid treatment varies greatly (ranging from 173 h to 619 h), and immunosuppressant accumulation occurs from the 9th day, with the trough concentration of tacrolimus increasing to 10 ng/ml and the trough concentration of cyclosporine increasing to 300 ng/ml [30]. Paxlovid contains ritonavir, an inhibitor of the CYP3A enzyme of the cytochrome P450 system [32]. The interaction between ritonavir and CYP3A-dependent drugs can cause the area under the blood concentration curve of the latter to increase significantly by several times, which may lead to significant drug interactions and risks of harm for patients with KD [30, 31]. Many immunosuppressants including cyclosporine, tacrolimus, and rapamycin, are highly dependent on CYP3A metabolism; therefore, the effect of Paxlovid on each drug must be considered [33, 34].

This study is the first to reveal the safety of Azvudine in COVID-19 patients with KD. We found no difference in the incidence of most adverse events between the Azvudine and Paxlovid groups, and the Azvudine group had a significantly lower incidence of hypophosphatemia and hypokalemia during the observation period. Therefore,

we have demonstrated for the first time that the safety of Azvudine in COVID-19 patients with KD is not inferior to that of Paxlovid, and that the incidence of hypophosphatemia and hypokalemia is lower.

Previous studies have confirmed that the absolute value of lymphocytes in COVID-19 patients is significantly lower than that in healthy controls. A study from Wuhan, China, reported that 26 of 41 patients had lymphocytopenia, which can be used to predict patient outcomes [7, 35]. A unique immunological feature of SARS-CoV-2 infection is changes in the distributions of peripheral blood lymphocyte subsets. Reduced CD4 + T cells, CD8 + T cells, and NK cell exhaustion have been observed in COVID-19 patients [36, 37]. Studies in rats and rhesus monkeys have indicated that oral administration of Azvudine can lead to a high concentration of the active form in the thymus and that phosphate metabolites can also be found in peripheral blood lymphocytes. Paxlovid may treat COVID-19 mainly by inhibiting SARS-CoV-2 in the lungs (and epididymis), whereas Azvudine may cure COVID-19 by inhibiting SARS-CoV-2 in the thymus. A rhesus monkey study revealed that CD4+, CD8+, and NKT cells in the thymus were protected after Azvudine treatment, and that immune enhancement effects occurred [18, 22, 23]. In this study, Azvudine significantly increased lymphocyte counts compared with Paxlovid in COVID-19 patients with KD. We believe that enhancing the immune effect may be another potential advantage of Azvudine over Paxlovid.

In the past four years, SARS-CoV-2 has continued to mutate, and multiple mutant strains have emerged, including alpha, beta, gamma, delta, epsilon, and omicron strains [38–40]. Although the WHO announced that COVID-19 was no longer considered a Public Health Emergency of International Concern and the Chinese government has abolished the "zero crown" policy, cases of reinfection continue to appear [41, 42]. Many patients still require antiviral drugs to fight SARS-CoV-2. The risk of reinfection and severe illness in patients is still greater than that in healthy people. Considering the long-term high medical expenses of renal replacement therapy for KD patients and immunosuppressants after kidney transplantation, Azvudine, which is priced at only one-tenth that of Paxlovid, has a clear advantage in price.

This study has several limitations. First, this study did not obtain the vaccination information of the participants, which may have ignored the impact of the COVID-19 vaccine on medication. Considering that the coverage rate of COVID-19 vaccines in China has reached 92.54% [43, 44], we expect that incorporating vaccination status would have little impact on the results of this study. Second, no information regarding immunosuppressants was obtained, which may have influenced the findings of this study. Third, the finding that the lymphocyte population in the azvudine group was significantly greater than that in the Paxlovid group in this study requires further research to clarify the mechanism underlying this phenomenon. Finally, this study may have selection bias, information bias, and confounding bias due to the retrospective nature of the study. This study used propensity score matching to reduce confounding bias to a large extent. In addition, we included 9 hospitals in different regions and levels, checked patient diagnosis and medication information multiple times, classified the severity of disease, and constructed a flow chart for the screening of research subjects to reduce selection bias and information bias to a certain extent. The above measures can reduce the bias caused by the nature of retrospective studies, but they cannot be completely avoided.

Conclusions

This study is the first to reveal the safety and effectiveness of azvudine in COVID-19 patients with KD on the basis of a large, multicenter, real-world cohort study, which revealed that the safety and effectiveness of azvudine were not inferior to those of Paxlovid for treating COVID-19 patients with KD. This study provides more options for the antiviral treatment of COVID-19 patients with kidney disease.

Abbreviations

KD	Kidney disease
COVID-19	Corona Virus Disease 2019
AE	Adverse event
PSM	Propensity scores matching
HRs	Hazard ratios
Cis	Confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10643-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Author contributions

Zujiang Yu and Zhigang Ren designed the study. Silin Li, Donghua Zhang, Hong Luo, Guowu Qian, Ling Wang, Shixi Zhang, Guotao Li, Guangming Li, Zujiang Yu and Zhigang Ren managed the patients. Benchen Rao, Mengzhao Yang, Daming Wang, Chunyu Zhao and Ming Cheng collected the data. Benchen Rao, Daming Wang, Mengzhao Yang and Chunyu Zhao analyzed the data. Zhigang Ren and Benchen Rao wrote this manuscript. All authors reviewed and approved the final manuscript. Benchen Rao and Daming Wang

contributed equally to this study. The authorship order among the co–first authors was assigned based on workload and manuscript preparation.

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Data availability
The raw data used and analyzed in this study are included in the Supplementary Tables 2 and Supplementary Table 3. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
The ethics committee of The First Affiliated Hospital of Zhengzhou University approved this study (2023-KY-0865-001). Considering that this study was a retrospective study, and all patients were anonymous, the ethics committee of the First Affiliated Hospital of Zhengzhou University waived individual informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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